REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representatives David Devernoe at (858) 720-7943 or Gregory Einhorn at (858) 720-5133.

a. **Status of the Claims**

Pending claims

Claims 31, 34, 35, 114, 115, 132-154 and 189-200 are pending.

Claims added and amended in the instant amendment

The first occurrence of 152 is canceled, without prejudice, and claim 201 is added. After entry of the instant amendment, claims 31, 34, 35, 114, 115, 132 to 154 and 189 to 201 are pending and under consideration.

Outstanding Rejections

Claims 31, 34, 114, 115, 134, 140-154 and 189-200 stand rejected under 35 U.S.C. §112, second paragraph. Claims 31, 34, 114, 115, 134, 140-154 and 189-200 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Claims 134, 135 and 193, stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims. The Applicants respectfully note that all pending claims are free of the cited art.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims directed to methods for making a polypeptide polymer made by self-assembly of monomers, wherein at least one monomeric polypeptide of the plurality of

monomeric polypeptides has a modification comprising attachment of an enzyme, attachment of a nucleotide or attachment of a nucleotide derivative or attachment of a lipid or attachment of a lipid derivative or attachment of a targeting vector, can be found, inter alia, in paragraph spanning pages 7-8.

Claim Objections

Claims 152 and 153 are objected to as allegedly in improper dependent form for failing to further limit the subject matter of the previous claim. In addition, the Office indicates that there are two occurrences of claim 152 in the present claims. The first occurrence of claim 152 is canceled herein.

Applicants wish to clarify that claim 152 further limits claim 31, because claim 31 does not comprise attaching the polymer to a hydrogel. Claim 153 further limits claim 152 because the hydrogel need not comprise a three-dimensional structural network for a biochip.

Issues under 35 U.S.C. §112, second paragraph

Claims 31, 34, 114, 115, 134, 140-154 and 189-200 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention.

The Office alleged that the structure of monomeric polypeptide is not clear in claim 31. The present amendment of claim 31 addresses this rejection. In amended claim 31, at least one monomeric polypeptide of the plurality of monomeric polypeptides includes a modification.

With respect to claim 34, the Office alleged that it is not clear whether a polynucleotide encodes a monomeric polypeptide (e.g., SEQ ID NO:2) or a conjugate of polypeptide with nucleotide or lipid. The present amendment of claim 34 addresses this rejection. The nucleic acid encodes a monomeric polypeptide. The description of the monomeric polypeptide is clarified in currently amended claim 31.

With regard to claims 134 and 135, the Office alleged that "it is not clear whether the polymer structures addressed in the claims form from polymerization of polypeptide . . . or a conjugate of the polypeptide with nucleotide or lipid . . ." The present amendment of claim 31 addresses this rejection.

The Patent Office also alleges that in claim 135 "it is not clear whether the precise dimensions of peptide tube recited in the claim address any polypeptide or polymer of some particular monomeric polypeptide." To address the Office's concern, Applicants wish to clarify that hollow tube that is the subject of the specifically recited dimensions is formed by polymerization of the monomeric polypeptides by a self-assembly process, wherein the each monomeric polypeptide has either an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, or SEQ ID NO:10, or, (b) an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, or SEQ ID NO:10 having at least one conservative substitution. The amendment to claim 31 also addresses this issue.

With regard to claims 150 [149] to 152 the Office alleges that a redundancy is present related to the attachment of a targeting molecule to a monomeric polypeptide because it is not clear how attaching of a targeting molecule can be recited as a further step if now amended claim 31 requires that such targeting molecule is attached to a monomeric polypeptide before the process of polymerization. Claim 150 is directed to the method of claim 145, further comprising attaching a targeting molecule or a vector to the therapeutic agent- or drug-loaded polymer during the encapsulation process or after the completion of the encapsulation process.

Applicants respectfully aver that claim 150 is not redundant to amended claim 31. For example, amended claim 31 is directed to a method wherein at least one monomeric polypeptide of the plurality of monomeric polypeptides includes a modification comprising attachment of an enzyme, attachment of a nucleotide or attachment of a nucleotide derivative, or attachment of a lipid or attachment of a lipid derivative, or attachment of a targeting molecule or targeting vector. Claim 31 does not require attachment of a targeting molecule or targeting vector; these are only two possible species of attachments. Thus, the step of claim 150 could be attaching a targeting molecule

or targeting vector to a polymeric structure comprising, e.g., an enzyme, a nucleotide and/or a lipid. Furthermore, the step of claim 150 could be attaching a targeting molecule or targeting vector to the therapeutic agent. Additionally, the step of claim 150 could be attaching a different targeting molecule or targeting vector to the polymeric structure. Alternatively, the step of claim 150 could be attaching additional, but the same, targeting molecules or targeting vectors at a different (later) step in the process.

The Office also alleges that there is a discrepancy in selected claim terminology between claims 31 and 197 to 200 versus claim 150. The instant amended addresses this issue.

With regard to claim 193, the Patent Office is concerned that it may not be clear whether the polymer comprises a nanoscale delivery device or whether the polymer is, itself, the nanoscale delivery device. Claim 193 recites "wherein the polypeptide polymer comprises a nanoscale delivery vehicle." Applicants wish to clarify that the method of claim 31 does not necessarily result in the generation of a nanoscale delivery vehicle; this is only one alternative product made by the method. Following the doctrine of claim differentiation, claim 193 is directed to one of many alternative products generated by the method of claim 31.

Issues under 35 U.S.C. §112, first paragraph

Enablement

Claims 31, 34, 114, 115, 134, 140, 154 and 189 to 200 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The Office has specifically alleged that "there is no evidence that peptide SEQ ID NO:2 is capable of self-assembling into polymers." In this regard, the Office points to Example 20 and indicates that this example merely describes the "polymerization of a crude mixture of proteins obtained from E.Coli." Further, the Office submits that "[t]here is no evidence that the resulting product [of Example 20] is a polymer of a peptide . . .." The Office additionally asserts that the

specification lack guidance on the conditions of polymerization allowing self-assembly of SEQ ID NO:2.

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The adequacy of a disclosure for meeting the enabling requirement of 35 USC § 112 varies with a number of factors including the predictability of the art and the breadth of the claims. *In re Wands*, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In general, the stringency of the enablement requirement increases with the unpredictability of the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ (BNA) 18, 24 (CCPA 1970). However, even in an unpredictable art, "applicants are not required to disclose every species encompassed by their claims," *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d (BNA) 1438, 1445 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ (BNA) 214, 218 (CCPA 1976)), but the disclosure must be sufficient to teach one skilled in the art "how to make and . . . use the invention as broadly as it is claimed." *Id.* And, the scope of enablement need only present a reasonable correlation to the scope of the claims. *See e.g., In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Nevertheless, not everything necessary to practice the invention need be disclosed, what is well-known may be omitted. *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Respectfully, the Applicants redirect the Office's attention to the specification, as filed, in addition to the Declaration of Nelson Barton (included herewith). The specification demonstrates that the peptide of SEQ ID NO:2 is capable of self-assembly into polymers. For example, Figure 1 shows a transmission electron micrograph of one embodiment of a self-assembled protein of SEQ ID NO:2. *See also* page 100, lines 14-21. Example 19 describes reconstitution experiments evaluating CanA, CanB and CanC. *See* pages 146-8. In particular, this experiment describes evaluating polymerized cannulae from CanA for thermostability. *See* pages 147-8. CanA, of course, refers to SEQ ID NOs: 1 & 2. *See* page 117, lines 2-4. Example 20 describes the production and polymerization of CanA protein to form polymer fibers. See pages 149-151. The conditions of self-assembly of the protein of SEQ ID NO:2 into polymers fibers is described, in

particular, at pages 150-1. Respectfully, one of skill in the art would not interpret Example 20 as merely describing the "polymerization of a crude mixture of proteins obtained from E. coli extract." As declared by Dr. Barton, Example 20 contains two precipitation/centrifugation steps that purify the extract before polymerization. *See* pages 149-150 of the specification. Dr. Barton declares that the first precipitation is done by heat treatment, which denatures and precipitates the E. coli proteins, which are then removed by centrifugation -- leaving a soluble CanA fraction that self-assembles. In addition, Dr. Barton declares that Example 20 further describes an optional ammonium sulfate precipitation, followed by another centrifugation, which further purifies the supernatant/extract. As such, one of skill in the art could determine alternative conditions for self-assembly of monomers given the teachings in the specification. Page 151, lines 14-30 of the specification, clearly provides a description of the formation of polymer fibers comprised of monomeric protein subunits (in this example, the protein subunits comprise SEQ ID NO:2). These polymer fibers were produced by the process described in Example 20.

The Office also provides that:

> [e]ven if there has been demonstration of polymers obtained by self-assembly of peptide of SEQ ID NO:2, [the specification] does not reasonably provide enablement for polymers formed from conjugates of said monomeric polypeptide with lipids or nucleotide derivatives, or "targeting vectors" (e.g., oligosaccharides). It is well known that the process of self-assembly of polypeptide monomers into polymers depends critically on the structure of the monomers and even slight changes, such as change [sic] in length of chain, or addition of ionized residue may change the rate and/or direction of the reaction.

The Office cites a published article from 1992 (Urry et al.) and a published abstract (Jenekhe et al. 2000) in support of this allegation.

In response, the Applicants respectfully direct the Office's attention to Example 21, in addition to the Declaration of Nelson Barton (included herewith). Dr. Barton declares that one of skill in the art would understand how to make and use the presently claimed invention based on the present disclosure. As declared by Dr. Barton, Example 21 sets forth a method of preparing a polypeptide polymer (comprising tubules) utilizing a monomeric polypeptide of SEQ ID NO:2 together with a lipid. *See also* Figure 3; and page 101, line 12 to page 102, line 3. In addition, the

specification at pages 90-98 describes the attachment of targeting vectors and molecules on the monomeric polypeptide. *See also* Figure 2; and page 101, lines 7-11. Moreover, Dr. Barton further declares that one of skill in the art could determine alternative conditions to achieve self-assembly of the conjugated / modified monomers given the disclosure provided in the specification. Moreover, Dr. Barton declares that it was considered routine by one skilled in the art to determine what conditions to use or modify, including what modifications or attachments are possible or preferred, to produce a protein polymer tubule given the starting materials set forth in the present application.

As evidence that the present disclosure is enabling, Dr. Barton also provides experimental data in the form of an immunofluorescent light microscope image of nanotubules assembled from a fusion protein generated by fusing the CanA open reading frame (SEQ ID NO:1) to the open reading frame of the green fluorescent protein ZSGREEN(TM) (BD Biosciences Clontech, Palo Alto, Calif.). The nanotubules are comprised of monomeric polypeptide subunit conjugates of SEQ ID NO:2 attached to the green fluorescent protein. As declared by Dr. Barton, these tubules were formed under the self polymerization conditions set forth in Example 20.

In order to make a rejection, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the CCPA, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble

and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, rev. 2, May 2004, pg 2100-189.

The Office must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The Office should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. MPEP §2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

Notwithstanding the Applicant's enablement-related comments above, the Applicants respectfully aver that the Office has not met his or her initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and specifically address, below, how the art used to support the Office's enablement rejection is not sufficient to rebut the presumptively enabled specification.

For example, neither of the references cited by the Office discuss the protein subunits of the present claims. Urry discusses the effects of changes in ionization, temperature and pH on hierarchical hydrophopic folding as it relates to signal transduction. A selection of pentapeptides, which do not appear to be related to the monomeric polypeptides of the present claims, are evaluated in this reference. Regardless, as indicated above, Urry was published in 1992, so it could hardly be representative of the state of the art at the time the present application was filed in 2001. Jenekhe provides an abstract that discusses the formation of functional mesostructures and acknowledges that many flexible-coil block copolymers can self-organize into nanostructures and mesophases even if they lack "rigid sequences" and well-defined "intermolecular interactions," which are supposedly required for controlling the three-dimensional shape necessary for "introducing functions" into the assemblies. Respectfully, neither of these references appear to cast doubt on the enabling disclosure set forth in the present application.

Written Description

Claim 193 [134 and 135] is rejected under 35 U.S.C. §112, first paragraph, as it allegedly contains subject matter not described in the specification in such as way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (noting that it appears claims 134 and 135 were a typographical error). The Office alleges that claim 193 introduces new matter because it uses the phrase "polymer comprises nanoscale delivery vehicle." The Office alleges that although the application does describe what a nanoscale delivery vehicle is, it purportedly does not teach that the polymer can comprise a nanoscale delivery vehicle.

In response, the Applicants respectfully direct the Office's attention to the specification at page 3, lines 17-18 (one object of the invention is to form a nanoscale drug delivery vehicle); Figure 2 (process for encapsulating a drug in a nanoscale delivery vehicle); page 89, lines 17-20 (polymer used in a nanoscale delivery vehicle); page 98, lines 6-8; page 101, lines 7-11; etc. As such the phrase "polymer comprises nanoscale delivery vehicle" finds ample support in the specification, as filed. Accordingly, withdrawal of this rejection is respectfully requested.

In light of the above remarks and the present claim amendments, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

CONCLUSION

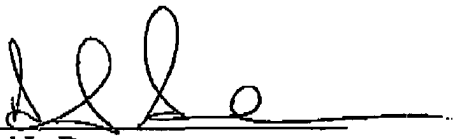
In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050 referencing docket no. 564462010900. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-7943 or Gregory Einhorn at (858) 720-5133.

Dated: August 27, 2004

Respectfully submitted,

By 

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